II. Remarks

A. Status of the claims

Claims 1, 2, 17 and 18 have been amended without prejudice. Support for the amendments can be found, e.g., on page 5, second paragraph, of the specification as filed and in the original claims.

New claims 20-23 have been added. Support for new claims 20-23 can be found, e.g., on page 2, fourth paragraph, of the specification as filed.

Claims 1, 2 and 5-23 are pending. It is respectfully submitted that no new matter has been added by virtue of present amendments.

B. Rejection under 35 U.S.C. § 102

Claims 1, 2, 5-13 and 16 were rejected under 35 U.S.C. § 102(b) over U.S. 5,149,538 to Granger et al.

The rejection is respectfully traversed.

It appears that the Examiner takes a position that disclosure of naloxone in the Granger patent reads on the "nauseants" in the independent claims 1 and 2. *See Office Action, page 4, where the Examiner stated that the compounds of the Granger patent "include nauseants such as naloxone."* Applicant submits that naloxone is not a nauseant, rather it is an opioid antagonist that does not necessarily produce nausea as one of its side effects (i.e. it is not a nauseant per se). Applicant therefore submits that this disclosure of the Granger patent does not destroy the novelty of independent claims 1 and 2.

As correctly stated by the Examiner in the Office Communication mailed on August 21, 2003:

> ... Granger et al (USPN 514,9538), discloses a transdermal formulation, which deters misuse, yet no distressing compounds are present ...

Office Communication mailed on August 21, 2003, page 5.

Further, in the Office Communication mailed on August 9, 2007, the Examiner acknowledged that the Granger patent "does not teach the use of an emetic, nauseant, flavoring substance, ergolide, bitter quaternary ammonium compound, or atropine as a distressing agent in a transdermal formulation of an opioid analgesic." *See Office communication mailed on August 9, 2007, page 3.*

The Granger patent therefore cannot anticipate the present claims because it does not describe each and every element of the present claims (e.g., "a distressing substance" as recited in independent claims 1 and 2).

Withdrawal of the anticipation rejection is respectfully requested.

C. Rejections under 35 U.S.C. § 103

1. U.S. Patent No. 5,149,538 to Granger et al. in view of U.S. Patent No. 5,891,919 to Blum et al. and U.S. Patent No. 4,175,119 to Porter

Claims 1, 2, 5-13 and 15-19 were rejected under 35 U.S.C. §103(a) over U.S. Patent No. 5,149,538 to Granger et al. ("the Granger patent") in view of U.S. Patent No. 5,891,919 to Blum et al. ("the Blum patent") and U.S. Patent No. 4,175,119 to Porter ("the Porter patent"). The Examiner stated that "the '538 patent discloses a transdermal formulation comprising opioid analgesics and distressing agents, the reference is however silent to the specific, emetic or bitters compounds of the instant claims." The Examiner then relied upon the Blum patent and the Porter patent to cure these deficiencies.

The rejection is respectfully traversed.

Applicants respectfully submit that the combination of the cited references does not disclose using a distressing substance in a dosage form to cause an abuser's distress concurrently with the achievement of an euphorigenic effect.

The Granger patent states that the described compositions contain an amount of the antagonist to attenuate the euphorigenic of the opioid. The attenuation of the euphorigenic effect of the opioid is achieved because the opioid antagonist competes with the opioid to bind to selected receptors and prevents the opioid's binding to these receptors. In other words, the Granger patent teaches to use the opioid antagonist to prevent the effect of the opioid (i.e., euphorigenic effect (i.e. a high)), rather than cause an additional reaction (i.e., a distressful reaction). In fact, the Granger patent does not even mention "a distressful reaction."

Applicant submits that the functional mechanism by which the Granger patent seeks to minimise abuse is based on this specific physiological interaction (i.e., *in vivo* blockage of opioid receptors). Applicant further submits that the agents described in the Blum patent and the Porter patent are incapable of this physiological interaction, as they act through different physiological mechanisms. Accordingly, the Granger patent (alone or in combination the Blum patent and the Porter patent) does not provide a reason for one skilled in the art to substitute the antagonists of the Granger patent with substances of the Blum patent and the Porter patent, because substances of the Blum patent and the Porter patent are not opioid antagonists, and therefore are not functional equivalents of the antagonists of the Granger patent.

Further, the purported substitution would render the Granger patent unsuitable for its intended purpose (i.e., to attenuate the euphorigenic effect of the opioid by use of an opioid antagonist), as it will change the abuse resistance mechanism taught by the Granger patent. The combination of the cited references does not therefore suggest the purported substutution. *See, e.g., MPEP, Section 2143.01 ("[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended*

purpose, then there is no suggestion or motivation to make the proposed modification ... ").

In response to the Examiner's statement that "the '538 patent discloses a transdermal formulation comprising opioid analgesics and distressing agent," Applicant notes that the Granger patent is directed to transdermal dosage comprising opioid analgesics in combination with opioid antagonists, rather than with distressing agents.

In response to the Examiner's statement that "if the purpose of the antagonist is to attenuate the euphoric properties of the opioid analgesics, this could be achieved by adding bitter/spicy and otherwise caustics compounds to the formulations," Applicant notes that, as discussed above, the attenuation of the euphorigenic effect taught in the Granger patent limits or prevents the euphorigenic effect from occurring by interacting with the opioid receptors. Applicant submits that this interaction is patentably distinct from causing a distressing effect (e.g., vomiting) as recited in the present claims.

In response to the Examiner's statement that "[t]hese distressing and caustic compounds would severely reduce the euphoric effects of any opioid compound associated with it," Applicant submits that these compounds will cause a distressing effect rather than prevent/block the euphoric effect of the opioid.

To advance prosecution and to further clarify the differences between the cited references and the presently claimed compositions for percutaneous administration, independent claims 1, 2, 17 and 18 were amended without prejudice to recite that the claimed compositions comprise an effective amount of a distressing substance such that a distressful reaction is produced when the claimed compositions are ingested orally or are administered as a parenteral bolus injection.

Applicant submits that the cited references do not suggest incorporation of an effective amount of a distressing substance into a composition for percutaneous

absorption as recited in the present claims, and therefore do not render the presently claimed compositions obvious.

Withdrawal of the obviousness rejection is respectfully requested.

2. U.S. Patent No. 5,149,538 to Granger et al. in view of U.S. Patent No. 46,001,390 and Drugs: Facts and Comparisons, entry for Pergolide Mesylate, pages 1621-1624

Claims 1, 10 and 14-15 were rejected under 35 U.S.C. § 103(a) over the Granger patent in view of U.S. Patent No. 6,001,390 to Yum et al. ("the Yum patent") and Drugs:Facts and Comparison, entry for Pergolide Mesulate, pages 1621-1624.

The rejection is respectfully traversed.

At the outset, Applicant respectfully notes that a copy of the Drug textbook relied upon in interposing the rejection was not enclosed with the Office Action. Applicant respectfully requests that a copy of the Drug textbook be provided, if the rejection is to be maintained.

Independent claim 1 has been amended without prejudice to recite that the distressing substance "does not penetrate the skin of a human patient when the composition is applied to the skin of said patient."

In response to the Examiner's statement that "pergolides do not readily permeate through the skin and require permeation enhancers," Applicant notes that the purported purpose of the Yum patent is to improve pergolide's permeability through the skin. The Yum patent therefore does not suggest a composition wherein "the distressing substance does not penetrate the skin of a human patient when the composition is applied to the skin of said patient" as recited in amended claim 1.

In response to the Examiner's statement that "[i]t would have been obvious to include the pergolide into the transdermal formulation of the '538 since they are similar formulations with similar components, Applicant submits that pergolide is not a functional equivalent of opioid antagonist. Further, the described utilities of the two references are different. The cited references therefore do not disclose "similar formulations with similar components."

In response to the Examiner's statement that pergolide salts "would have been obvious addition to an aversion formulation," Applicant submits that the cited references do not mention "distressing the abuser." Rather, as discussed above, the aim of the Granger patent is to prevent the user from achieving an euphorigenic effect (i.e. a high). The cited references therefore do not suggest the purported "addition." Applicant further asserts that this purported "addition" is based on the impermissible use of hindsight learned from the present specification.

The cited references also do not render the present claims obvious for the additional reasons articulated above with regard to the obviousness rejection over the combination of the Granger patent with the Blum patent and the Porter patent.

For the foregoing reasons, withdrawal of the obviousness rejection is respectfully requested.

III. CONCLUSION

An early and favorable action is earnestly solicited. In view of currently recommended Patent Office policy, the Examiner is invited to contact the undersigned in the event that a telephonic interview would advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Oleg Ioselevich
Reg. No. 56,963

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018
(212) 736-1940